

**SECOND PAIR OF EYES
WORKSHEET**

SERIAL NUMBER: **10714577**

EXAMINER: **Desai, R**

DATE: **31 Dec 2005**

ACTION(S) REVIEWED

allowance

NOTES:

1. IF A CLEAR ERROR COULD BE CHARGED UNDER TWO OR MORE OF: PATENTABILITY DETERMINATION; ACTION TAKING; OR PATENT EXAMINING FUNCTIONS, IT IS ONLY CHARGEABLE ONCE, UNDER THE FIRST APPROPRIATE LISTED CATEGORY.
2. IN A GIVEN OFFICE ACTION IT IS POSSIBLE TO HAVE TWO OR THREE CLEAR ERRORS, IF THEY ARE BASED ON UNRELATED(DIFFERENT ERRORS), AND ARE CHARGED IN DIFFERENT CATEGORIES.
3. ONLY ONE PATENTABILITY DETERMINATION AND/OR ACTION TAKING AND/OR PATENT EXAMINING FUNCTIONS ERROR IS CHARGEABLE AGAINST AN EXAMINER IN A SINGLE OFFICE ACTION.
4. IN AN APPLICATION WHERE MORE THAN ONE OFFICE ACTION IS BEING REVIEWED IT IS POSSIBLE TO HAVE A PATENTABILITY DETERMINATION AND/OR AN ACTION TAKING AND/OR PATENT EXAMINING FUNCTIONS ERROR IN EACH OFFICE ACTION.
5. IF THE EXAMINER HAS REPEATED THE SAME ERROR IN TWO OFFICE ACTIONS IN AN APPLICATION IN THE REVIEW PERIOD, TWO ERRORS SHOULD BE CHARGED AGAINST THE EXAMINER.

Abbreviations: Office Action = OA

Not Applicable = N/A

PATENTABILITY DETERMINATION

<u>A. MAJOR ACTIVITIES</u>	YES	NO	COMMENTS
a. ALL CLAIMS PATENTABLE (UNDER 35 USC 102 & 103), OVER ALL ART OF RECORD	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
b. ARE ALL CLAIMS PATENTABLE (UNDER 35 USC 102 & 103) OVER ALL ART WHICH IS NOT OF RECORD BUT SHOULD BE	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
c. ARE ALL CLAIMS PATENTABLE UNDER ALL OTHER PERTINENT SECTIONS OF THE STATUTE (e.g., 101, 102, 103, 112, 251, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
d. ARE ALL CLAIMS PATENTABLE UNDER ALL NONSTATUTORY REJECTIONS (e.g., OBVIOUSNESS TYPE DOUBLE PATENTING)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p><input type="checkbox"/> The ODP rejections should not have been dropped. A comparison of the claims shows there is overlapping claimed subject matter. See for example, claim 1 in the '497 patent and current application claim 1.</p> <p><input type="checkbox"/> See also the '899 patent</p> <p>The ODP was made and dropped but the claims do not appear to reflect the nonoverlap of claimed subject matter as argued in applicant's response.</p>
<u>B. IS THERE A "CLEAR ERROR" COMMITTED</u>			
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
<u>C. SUPPORTING EXPLANATION</u>			

Issue classification sheet has box "X" marked for claims numbered as presented by applicant presented with final claim numbers – if numbering incorrect will generate printer query.

ACTION TAKING

<u>A. MAJOR ACTIVITIES</u>	YES	NO	COMMENTS
a. DO ACTIONS INCLUDE ALL REASONABLE REJECTIONS, (MPEP 7.07(g))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
b. WERE ANY UNREASONABLE REJECTIONS MADE	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
c. WERE ANY UNREASONABLE FORMAL REQUIREMENTS MADE	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
d. DID THE EXAMINER TAKE ANY ARBITRARY OR CAPRICIOUS ACTION	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
e. IS THE RECORD, TAKEN AS A WHOLE, REASONABLY CLEAR AND COMPLETE, INCLUDING REASONS FOR ALLOWANCE WHERE NECESSARY	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
f. DO ACTIONS PROPERLY TREAT ALL MATTERS OF SUBSTANCE IN APPLICANT'S RESPONSE, INCLUDING AFFIDAVITS/DECLARATIONS, IF ANY	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<u>B. IS THERE A "CLEAR ERROR" COMMITTED</u> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No </div>			
<u>C. SUPPORTING EXPLANATION</u> <div style="border: 1px solid black; height: 20px; width: 100%; margin-top: 5px;"></div>			

PATENT EXAMINATION FUNCTIONS

<u>A. WERE THESE FUNCTIONS PROPERLY PERFORMED</u>	YES	NO	COMMENTS
1a. CHECKING APPLICATIONS FOR FORMAL MATTERS	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
1b. CHECKING APPLICATION FOR TECHNOLOGICAL ACCURACY	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2. TREATING DISCLOSURE STATEMENTS & STATEMENTS AND CLAIMS FOR PRIORITY	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
3. ANALYZING DISCLOSURE AND CLAIMS FOR COMPLIANCE TO 35 USC 112	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
4. PLANNING FIELD OF SEARCH	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
5. CONDUCTING SEARCH	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
6. FORMULATING REJECTIONS UNDER 102/103 OR DETERMINING HOW CLAIMS DISTINGUISH OVER PRIOR ART	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
7. DETERMINING WHETHER AMENDMENT INTRODUCES NEW MATTER	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
8. DETERMINING WHETHER RESTRICTION IS PROPER	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
9. DETERMINING OPERABILITY/UTILITY	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
10. EVALUATING/APPLYING CASE LAW	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
11. EVALUATING SUFFICIENCY OF AFFIDAVITS/DECLARATIONS	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
12. DETERMINING WHETHER APPROPRIATE LINE OF PATENTABLE DISTINCTION MAINTAINED BETWEEN APPLICATIONS &/OR PATENTS	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
13. EVALUATING SUFFICIENCY OF REISSUE OATH/DECLARATION	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
14. EVALUATING APPROPRIATENESS OF GROUNDS FOR REEXAMINATION	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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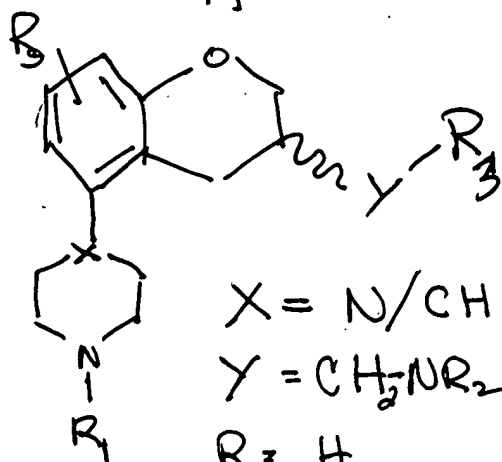
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1899



$X = N/CH$
 $Y = CH_2NR_2 \dots$

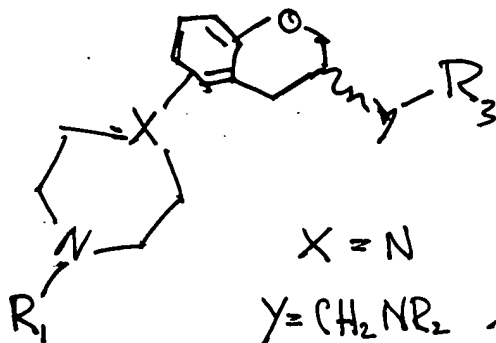
$R_1 = H$

$R_3 = C_1-C_6$ alkyl
 C_3-C_6 cycloalkyl

$(CH_2)_n$ -aromatic

one/2 hetero
 atoms of
 N, O, S

Cermond app



$X = N$

$Y = CH_2NR_2 \dots$

$R_1 = H$

$R_3 = (CH_2)_n$ Phenyl

mono/disub

~~C_{1-6}~~ of O, N, S, ...

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vacuo giving 950 mg of a crude product. Purification by column chromatography on silica gel using chloroform/methanol/concentrated ammonia 95:5:0.5 as the eluent afforded 154 mg (24% yield) of the title compound as an oil: EIMS (70 eV) m/z (relative intensity) 569 (3, M^{30}).

Example 48

(S)-N-[5-(4-Methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-[4-(2-hydroxyethyl)-piperazin-1-yl]benzamide

(S)-N-[5-(4-Methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-[4-(2-benzyloxyethyl)-piperazin-1-yl]benzamide (150 mg, 0.27 mmol) was dissolved in acetic acid (10 mL) and palladium (10%) on carbon (12 mg) was added. Hydrogenation at room temperature and at atmospheric pressure for 14 h followed by filtration and evaporation of the solvent in vacuo gave 180 mg of a crude product. The residue was partitioned between methylene chloride (60 mL) and 2 M NH_3 (5 mL) and washed with brine (5 mL). Drying ($MgSO_4$) the solution and evaporation of the solvent in vacuo gave 120 mg of crude material. Purification by preparative TLC on silica using chloroform/methanol/concentrated ammonia 95:5:0.5 as the eluent afforded 37 mg (29% yield) of the title compound as a white solid: mp 211–212° C.; EIMS (70 eV) m/z (relative intensity) 479 (8, M^{30}); $[\alpha]_D^{22}$ -26° (c 0.26, chloroform).

PHARMACOLOGY

Electrical Field Stimulation of [3H]-5-HT Release from occipital Cortices of Guinea Pigs

[3H]-5-HT is released by electrical field stimulation from slices of occipital cortices guinea pigs which have been pre-incubated with [3H]-5-HT. This release is similar to that caused by nerve stimulation, i.e. exocytotic release from serotonergic nerve terminals, depending on the presence of Ca^{2+} in the incubation medium. The 5-HT release is regulated at the level of the nerve terminals by autoreceptors, in the guinea pigs (like in humans) belonging to the h5-HT_{1B} receptor subtype. Thus, agonists of h5-HT_{1B} receptors reduce the amount of [3H]-5-HT released by electrical field stimulation whereas the release is increased by antagonists of this receptor type. Testing compounds with this method is accordingly a convenient screening technique for determining the potency and functional effect of new h5-HT_{1B} receptor agonists and antagonists.

METHODS AND MATERIALS

Buffer composition (mM) $NaHCO_3$ (25), $NaH_2PO_4 \cdot H_2O$ (1.2), $NaCl$ (117), KCl (6), $MgSO_4 \cdot 7H_2O$ (1.2), $CaCl_2$ (1.3); $EDTA Na_2$ (0.03). The buffer is gassed for at least 30 min before use. The pH of the buffer is about 7.2 in the room temperature but it rises to about 7.4 at 37° C.

Preparation of Occipital Cortical Slices

Guinea pigs (200–250 g) were decapitated and the whole brains were removed. The occipital cortices were dissected and cut to slices 0.4×4 mm with McIlwain chopper machine. The white part of the tissue should be removed carefully with a tweezer before slicing. The slices were incubated in 5 ml buffer in the presence of 5 mM pargyline chloride. After incubation with 0.1 mM [3H]-5-HT for another 30 min the slices were transferred to a test tube and washed three times with same volume buffer. The slices were transferred to the superfusion chambers with a plastic pipette and were washed for 40 min with the buffer in the presence of uptake inhibitor citalopram 2.5 μM with a flow 0.5 ml/min.

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Electrical Stimulation of 5-HT Release

The superfused buffer was collected in 2 mL/fraction. The slices were stimulated by electricity with a train of pulses of frequency 3 Hz, duration 2 ms and current 30 mA for 3 min at the 4th and 13th fractions. The tested drugs were added from the 8th fraction to the end of experiment.

RESULTS

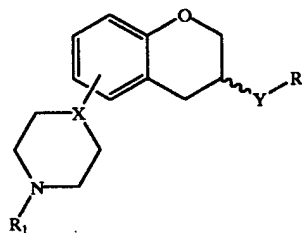
A first electrical (or K^+) stimulation results in a standard amount of [3H]-5-HT released (S_1). Before the first and the second stimulation the h5-HT_{1B} antagonist is added to the media which results in a dose dependent increase of the release (S_2) after the second stimulation. See FIG. 1.

The S_2/S_1 ratio which is the per cent of released [3H]-5-HT at the second stimulation (S_2) divided by that of the first stimulation (S_1), was used to estimate drug effects on transmitter release.

What is claimed is:

1. A compound of formula (I)

(I)



wherein

✓ X is N;

✓ Y is CH_2NR_2 , NR_2CO , $CONR_2$, NR_2SO_2 or NR_2CONR_2 wherein R_2 is H or C_1 - C_6 alkyl;

✓ R_1 is H or C_1 - C_6 alkyl;

✓ R_3 is $(CH_2)_n$ -phenyl, wherein the phenyl may be mono- or di-substituted with R_4 and/or R_5 ; wherein R_4 is selected from the group consisting of

- a) H,
- b) C_1 - C_6 alkyl,
- c) C_3 - C_6 cycloalkyl,
- d) halogen,
- e) CN,
- f) CF_3 ,
- g) OH,
- h) C_1 - C_6 alkoxy,
- i) NR_6R_7 ,
- j) OCF_3 ,
- k) SO_3CH_3 ,
- l) SO_3CF_3 ,
- m) $SO_2NR_6R_7$,
- n) phenyl,
- o) phenyl- C_1 - C_6 alkyl,
- p) phenoxy,
- q) C_1 - C_6 alkylphenyl,

r) an optionally substituted 5- or 6-membered heterocyclic ring containing one or two heteroatoms which is (are) N, wherein the substituent(s) is (are) selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, phenyl- C_1 - C_6 alkyl, $(CH_2)_mOR_9$ wherein m is 2–6 and R_9 is H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or phenyl- C_1 - C_6 alkyl, and COR_9 ,

s) C_1 - C_6 alkoxy,

t) OCF_3 ,

u) SO_3CH_3 ,

v) SO_3CF_3 ,

w) $SO_2NR_6R_7$,

x) phenyl,

y) phenyl- C_1 - C_6 alkyl,

z) phenoxy,

aa) C_1 - C_6 alkylphenyl,

ab) an optionally substituted 5- or 6-membered heterocyclic ring containing one or two heteroatoms which is (are) N, wherein the substituent(s) is (are) selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, phenyl- C_1 - C_6 alkyl, $(CH_2)_mOR_9$ wherein m is 2–6 and R_9 is H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or phenyl- C_1 - C_6 alkyl, and COR_9 ,

ac) C_1 - C_6 alkoxy,

ad) OCF_3 ,

ae) SO_3CH_3 ,

af) SO_3CF_3 ,

ag) $SO_2NR_6R_7$,

ah) phenyl,

ai) phenyl- C_1 - C_6 alkyl,

aj) phenoxy,

ak) C_1 - C_6 alkylphenyl,

al) an optionally substituted 5- or 6-membered heterocyclic ring containing one or two heteroatoms which is (are) N, wherein the substituent(s) is (are) selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, phenyl- C_1 - C_6 alkyl, $(CH_2)_mOR_9$ wherein m is 2–6 and R_9 is H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or phenyl- C_1 - C_6 alkyl, and COR_9 ,

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s) an optionally substituted 5- or 6-membered heteroaromatic ring containing one or two heteroatoms which is (are) N, wherein the substituent(s) is (are) selected from the group consisting of C₁-C₆ alkyl, C₃-C₆ cycloalkyl and phenyl-C₁-C₆ alkyl, and

t) COR₈;

wherein R₆ is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl; R₇ is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl; and R₈ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, CF₃, NR₆R₇ or phenyl;

R₅ is selected from the group consisting of H, OH, CF₃, OCF₃, halogen, C₁-C₆ alkyl and C₁-C₆ alkoxy;

and n is 0-4;

wherein the compound is an (R)-enantiomer, an (S)-enantiomer, or a racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof.

2. The compound according to claim 1 wherein Y is NR₂CO or CONR₂.

3. The compound according to claim 1, wherein the phenyl ring of substituent R₃ is substituted with R₄, and R₄ is an optionally substituted 5- or 6-membered heterocyclic or heteroaromatic ring containing one or two heteroatoms which is (are) N; or COR₈.

4. The compound according to claim 1 or 3, wherein n is 0.

5. The compound according to claim 3 wherein R₈ is NR₆R₇.

6. The compound according to claim 2, wherein Y is NR₂CO.

7. The compound according to claim 1, wherein Y is NR₂CO and R₄ is COR₈.

8. A compound selected from the group consisting of

(S)-N-[5-(4-Methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-piperidinobenzamide;

(S)-N-[5-(4-Methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-butoxybenzamide;

(S)-N-[5-(4-Methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-trifluoromethylbenzamide;

(S)-N-[5-(4-Methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-N,N-diethylaminobenzamide;

(S)-N-[5-(4-Methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-trifluoromethoxybenzamide;

(S)-N-[5-(4-Methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-(4-piperidon-1-yl)benzamide; and

(S)-N-[5-(4-Methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-(4-benzylpiperazin-1-yl)benzamide

in the form of a free base or a pharmaceutically acceptable salt or solvate thereof.

9. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of claim 1 as an enantiomer or racemate, in the form of a free base or a pharmaceutically acceptable salt or solvate thereof optionally in association with diluents, excipients or inert carriers.

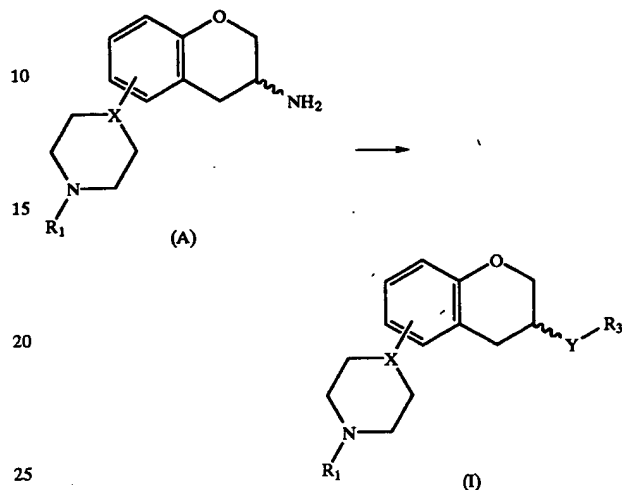
10. A method for the treatment of 5-hydroxytryptamine-mediated disorders, comprising administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical formulation of claim 9.

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11. A process for the preparation of the compound of formula I according to claim 1, comprising:

A(i)

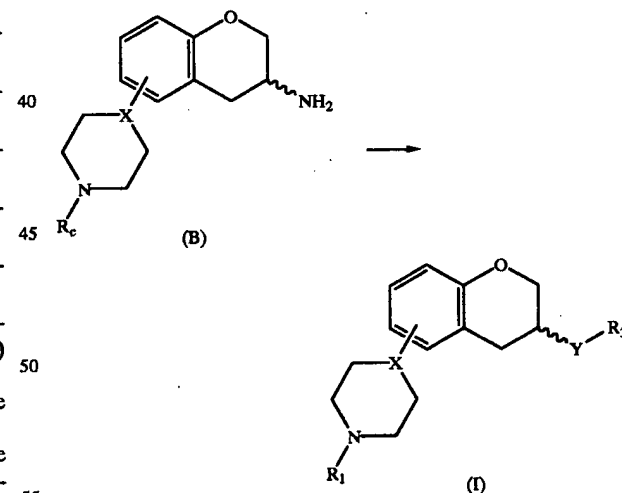
acylation, in the case wherein R₁ is C₁-C₆ alkyl, Y is NR₂CO, R₂ is hydrogen and X and R₃ are as defined in claim 1, of a compound of formula A



with an activated carboxylic acid R₃-COLg₁, wherein Lg₁ is a leaving group; or with a carboxylic acid R₃-COOH and an activating reagent; or

A(ii)

acylation, in the case wherein R₁ is hydrogen, Y is NR₂CO, R₂ is hydrogen, R_c is a protecting group and X and R₃ are as defined in claim 1, of a compound of formula B



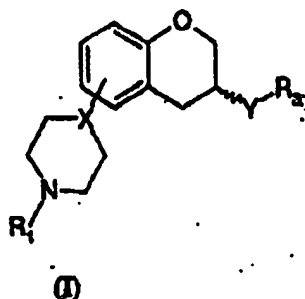
with an activated carboxylic acid R₃-COLg₁, wherein Lg₁ is a leaving group; or with a carboxylic acid R₃-COOH and an activating reagent, and removing the protecting group R_c.

* * * * *

In the claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (previously presented) A compound of formula (I)



wherein

✓ X is N;

✓ Y is CH_2NR_2 , NR_2CO , CONR_2 , NR_2SO_2 or NR_2CONR_2

wherein R_2 is H or $\text{C}_1\text{-C}_6$ alkyl;

✓ R_1 is H, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl;

✓ R_3 is $(\text{CH}_2)_n\text{-phenyl}$, wherein the phenyl is

monosubstituted with R_4 or disubstituted with R_4 and R_5 ;

wherein R_4 is selected from

a) an optionally substituted 5-, 6- or 7-membered heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 , wherein when the heterocyclic ring is 5- or 6-membered and contains one heteroatom, the heteroatom is not N and when the heterocyclic ring is 5- or 6-membered and contains two heteroatoms, the heteroatoms are not

both N and wherein the substituent(s) is(are)
selected from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, phenyl-
C₁-C₆ alkyl, (CH₂)_mOR₉, wherein m is 2-6 and R₉ is H,
C₁-C₆ alkyl, C₃-C₆ cycloalkyl or phenyl-C₁-C₆ alkyl,
and COR₈, and

b) an optionally substituted 5- or 6-membered
heteroaromatic ring containing one or two
heteroatoms selected from N, O and S, wherein when
the heteroaromatic ring contains one heteroatom,
the heteroatom is not N and when the heteroaromatic
ring contains two heteroatoms, the heteratoms are
not both N and wherein the substituent(s) is (are)
selected from C₁-C₆ alkyl, C₃-C₆ cycloalkyl and
phenyl-C₁-C₆ alkyl;
R₅ is selected from OH, CF₃, OCF₃, halogen, C₁-C₆
alkyl and C₁-C₆ alkoxy;

and n is 0-4;

wherein the compound is an (R)-enantiomer, an (S)-
enantiomer, or a racemate in the form of a free base or a
pharmaceutically acceptable salt or solvate thereof.

2. (Previously presented). The compound according to claim...

1 wherein Y is NR₂CO or CONR₂.

3. (cancelled)
4. (previously presented) The compound according to claim 1, wherein R_1 is H or C_1-C_6 alkyl.
5. (cancelled)
6. (cancelled)
7. (previously presented) The compound according to claim 1, wherein n is 0.
8. cancelled
9. (previously presented) The compound according to claim 2, wherein Y is NR_2CO .
10. (previously presented) The compound according to claim 1 wherein Y is NR_2CO and R_4 is morpholino.
11. (cancelled)
12. (previously presented) A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of claim 1 as an enantiomer or racemate, in the form of a free base or a pharmaceutically acceptable salt or solvate thereof optionally in association with diluents, excipients or inert carriers
13. (previously presented) A method for the treatment of α -hydroxytryptamine-mediated disorders, comprising

administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical formulation of claim 12.

14-26. (cancelled)

27. (previously presented) A method for the treatment of 5-hydroxytryptamine-mediated disorders comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound defined in claim 1.

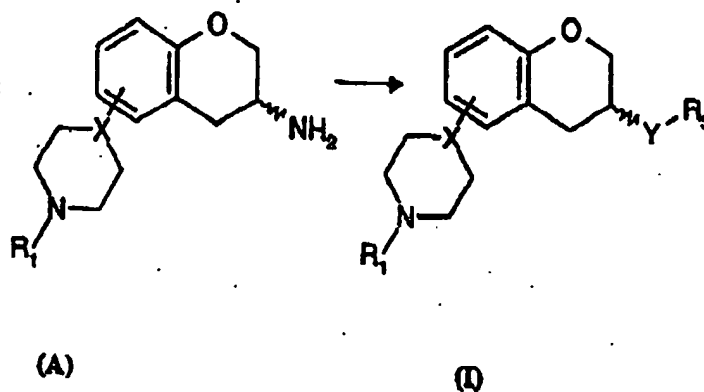
28. (previously presented) A method for the treatment of 5-hydroxytryptamine-mediated disorders in the central nervous system which require treatment with an h5-HT_{1B} antagonist, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound defined in claim 1.

29. (previously presented) A process for the preparation of the compound of formula I according to claim 1, comprising:

A(i)

acylation, in the case wherein R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl, Y is NR₂CO, R₂ is hydrogen and X and R₁ are as

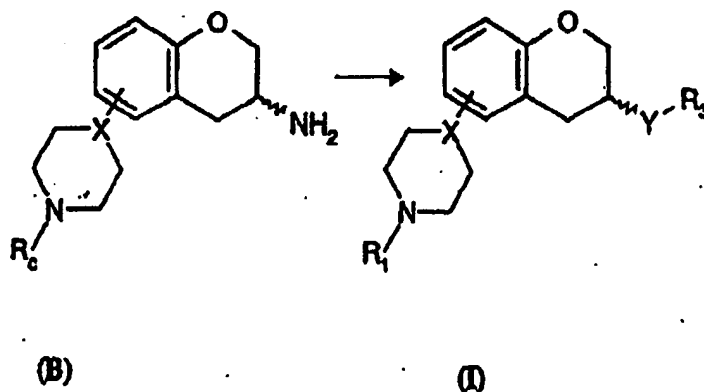
defined in claim 1, of a compound of formula A,



with an activated carboxylic acid R_3-COLg_1 wherein Lg_1 is a leaving group; or with a carboxylic acid R_3-COOH and an activating reagent;

A(ii)

acylation, in the case wherein R_1 is hydrogen, Y is NR_2CO , R_2 is hydrogen, R_c is a protecting group and X and R_1 are as defined in claim 1, of a compound of formula B

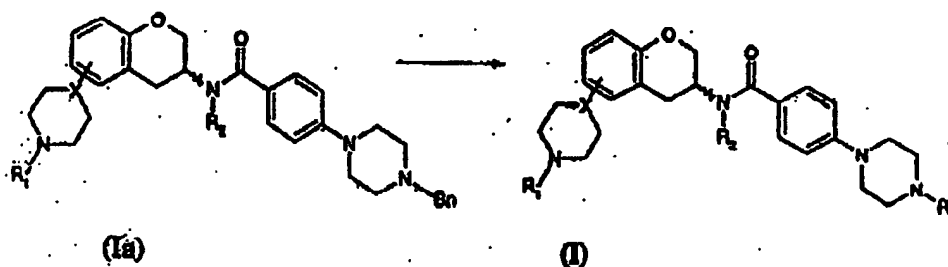


with an activated carboxylic acid R_3-COLg_1 wherein Lg_1 is a

leaving group; or with a carboxylic acid R_3 -COOH and an activating reagent, and removing the protecting group R_c ;

A(iii)

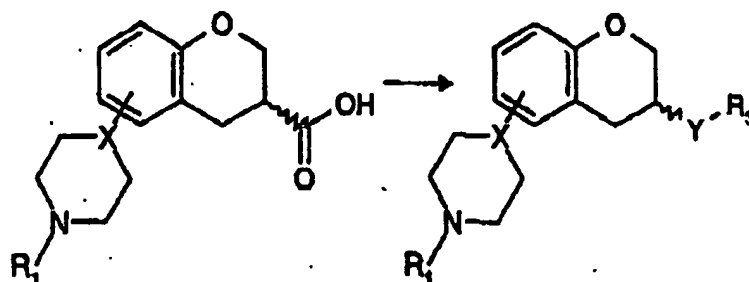
debenzylation, in the case wherein R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl, X and R_2 are as defined in claim 1 and R_3 below is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $(CH_2)_mOH$ wherein m is 2-6, or COR_4 , of a compound of formula Ia, followed by a) hydrogenation, b) alkylation, c) alkylation and removal of a protecting group or d) acylation;



B(1)

reacting, in the case wherein R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl, Y is $CONR_2$, and X, R_2 and R_3 are as defined in claim 1, an activated carboxylic

acid of a compound of formula C;



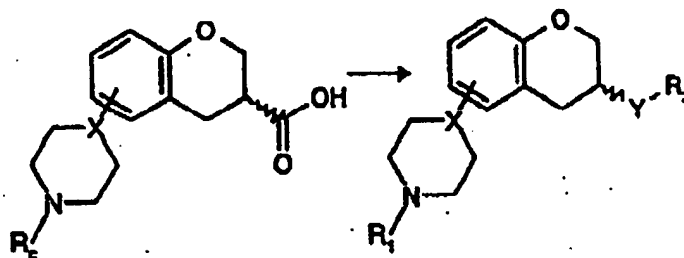
(C)

(I)

with an aniline or an amine HNR_2R_3 ; or

B(11)

reacting, in the case wherein R_1 is hydrogen, Y is NR_2CO , R_c is a protecting group and X , R_2 and R_3 are as defined in claim 1, an activated carboxylic acid of a compound of formula D



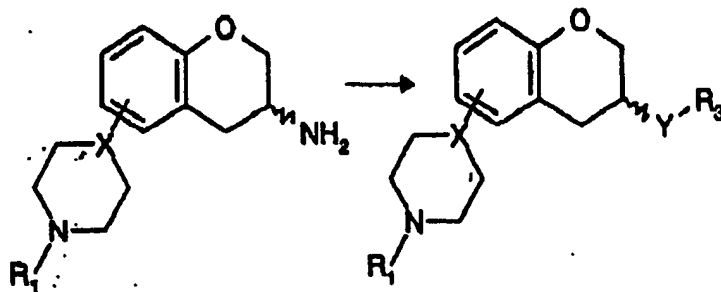
(D)

(I)

with an aniline or an amine HNR_2R_3 , and removing the protecting group R_c ; or

C

reacting, in the case wherein R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, Y is NR_2CONR_2 , R_2 is hydrogen and X and R_3 are as defined in claim 1, a compound of formula A,

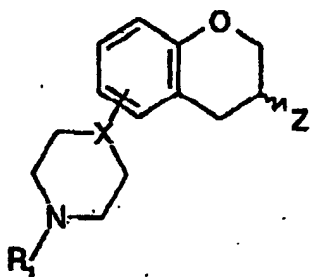


(A)

(I)

with a suitable azide in the presence of a carboxylic acid, R_3COOH .

30. (previously presented) A compound of the formula



wherein

$X=N$;

$Z=NH_2$ or $COOH$; and

R_1 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl.

31. (new) A method for modulating 5-HT neurotransmission comprising administering an effective amount of a compound according to claim 1.

32. (new) A method for modulating h5HT_{1B} receptor activity comprising administering an effective amount of a compound according to claim 1.

33. (new) The method according to any one of claims 13, 27 and 28, wherein the disorder is depression.

34. (new) The method according to claim 32 or 33 for treatment of depression.

REMARKS

Upon entry of the amendments herein, claims 1, 2, 4, 7, 9, 10, 12, 13 and 27-34 are pending in the application. No amendments have been made herein to the previously pending claims; however, new claims 31-34 have been added. No new matter has been introduced by these new claims.

Applicants and the undersigned acknowledge with gratitude the time taken by Examiner Desai on September 20, 2005 to discuss various issues and to reach a clearer understanding of the relationship between the presently claimed subject matter and that allowed in the previously filed applications in this family. Much of the presentation following is reflective of the issues discussed.

The rejection of claim 1 as being nonenabled was maintained in the present Office Action. As pointed out to the Examiner during the September 20th discussion, it is the relationship between the claimed subject matter of the instant application and that allowed in the grandparent application (Serial No. 09/171,570, now U.S. Patent No. 6,479,497) that is important, not the relationship between the instantly claimed subject matter and that allowed in the parent (Serial No. 10/285,743, now U.S. Patent No. 6,670,359). The claims allowed in the parent application are all directed to compounds wherein X is CH, whereas the claims in the present application are all directed to compounds wherein X is N. Accordingly, there is no

2.9 mmol) in *N,N*-dimethylformamide (10 mL) was added a solution of sodium dithionite (2.1 g, 12 mmol) in water (5 mL). The mixture was stirred at 55° C. for 3 h and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using ethyl acetate as the eluent affording 273 mg of the title compound (55% yield): EIMS (70eV) *m/z* (relative intensity) 383 (100, M⁺).

Example 20

N-(4—Morpholinophenyl)-8-methoxy-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-carboxamide

A solution of *N*-(4-morpholinophenyl)-5-amino-8-methoxy-3,4-dihydro-2H-1-benzopyran-3-carboxamide (270 mg, 0.7 mmol), bis (2-chloroethyl)-methylamine hydrochloride (288 g, 1.5 mmol) and sodium hydrogen carbonate (126 mg, 1.5 mmol) in *n*-butanol (10 mL) as stirred at 90° C. for 2.5 h. 2 M ammonia (10 mL) was added at 50° C., the mixture was cooled and the phases were separated. The organic phase evaporated in vacuo and the residue was purified by column chromatography on silica gel using ethyl acetate/triethyl amine (100:8) as the eluent affording 170 mg (50% yield) of the title compound as white crystals: mp 202–204° C.; EIMS (70eV) *m/z* (relative intensity) 466 (100 M⁺).

PHARMACOLOGY

Electrical field stimulation of [³H]-5-HT release from occipital cortex of guinea pigs

[³H]-5-HT is released by electrical field stimulation from slices of occipital cortex of guinea pigs which have been pre-incubated with [³H]-5-HT. This release is similar to that caused by nerve stimulation, i.e. exocytotic release from serotonergic nerve terminals, depending on the presence of Ca²⁺ in the incubation medium. The 5-HT release is regulated at the level of the nerve terminals by autoreceptors, in the guinea pigs (like in humans) belonging to the h5-HT_{1B} receptor subtype. Thus, agonists of h5-HT_{1B} receptors reduce the amount of [³H]-5-HT released by electrical field stimulation whereas the release is increased by antagonists of this receptor type. Testing compounds with this method is accordingly a convenient screening technique for determining the potency and functional effect of new h5-HT_{1B} receptor agonists and antagonists.

Methods and Materials

Buffer Composition (mM)

NaHCO₃ (25), NaH₂PO₄·H₂O (1.2), NaCl (117), KCl (6), MgSO₄·7H₂O (1.2), CaCl₂ (1.3), EDTA Na₂ (0.03). The buffer is gassed for at least 30 min before use. The pH of the buffer is about 7.2 in the room temperature but it rises to about 7.4 at 37° C.

Preparation of Occipital Cortical Slices

Guinea pigs (200–250 g) were decapitated and the whole brain was removed. The occipital cortex was dissected and cut to slices 0.4×4 mm with McIlwain chopper machine. The white part of the tissue should be removed carefully with a tweezer before slicing. The slices were incubated in 5 ml buffer in the presence of 5 mM pargyline chloride. After incubation with 0.1 mM [³H]-5-HT for another 30 min the slices were transferred to a test tube and washed three times with same volume buffer. The slices were transferred to the superfusion chambers with a plastic pipette and were washed for 40 min with the buffer in the presence of uptake inhibitor citalopram 2.5 μM with a flow 0.5 ml/min.

Electrical Stimulation of 5-HT Release

The superfused buffer was collected in 2 mL/fraction. The slices were stimulated by electricity with a train of pulses of

frequency 3 Hz, duration 2 ms and current 30 mA for 3 min at the 4th and 13th fractions. The tested drugs were added from the 8th fraction to the end of experiment.

Results

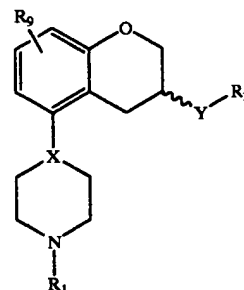
A first electrical (or K⁺) stimulation results in a standard amount of [³H]-5-HT released (S₁). Between the first and the second stimulation the h5-HT_{1B} antagonist is added to the media which results in a dose depending increase of the release (S₂) after the second stimulation. See FIG. 1.

The S₂/S₁ ratio which is the per cent of released [³H]-5-HT at the second stimulation (S₂) divided by that of the first stimulation (S₁) was used to estimate drug effects on transmitter release.

What is claimed is:

1. A compound of the formula I

(I)



wherein

X is N or CH;

Y is CH₂—NR₂, NR₂—CO, CO—NR₂ or NR₂SO₂ wherein R₂ is H or C₁–C₆ alkyl;

R₁ is H, C₁–C₆, alkyl or C₃–C₆ cycloalkyl;

R₃ is C₁–C₆ alkyl, C₃–C₆ cycloalkyl or (CH₂)_n-aromatic ring, wherein the aromatic ring is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from the group consisting of N, O and S and wherein the aromatic ring may be mono- or di-substituted with R₄ and/or R₅;

wherein R₄ is H, C₁–C₆ alkyl, C₃–C₆ cycloalkyl, halogen, CN, CF₃, OH, C₁–C₆ alkoxy, NR₆R₇, OCF₃, SO₃CH₃, SO₃CF₃, SO₂NR₆R₇, phenyl, phenyl—C₁–C₆ alkyl, phenoxy, C₁–C₆ alkylphenyl, an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O, S, SO and SO₂ wherein the substituent(s) is(are) selected from the group consisting of C₁–C₆ alkyl, C₃–C₆ cycloalkyl and phenyl—C₁–C₆ alkyl; or COR₈;

wherein R₆ is H, C₁–C₆ alkyl or C₃–C₆ cycloalkyl;

R₇ is H, C₁–C₆ alkyl or C₃–C₆ cycloalkyl; and

R₈ is C₁–C₆ alkyl, C₃–C₆ cycloalkyl, CF₃, NR₆R₇, phenyl, or a heterocyclic ring containing one or two heteroatoms, selected from the group consisting of N, O, S, SO and SO₂;

wherein R₅ is H, OH, CF₃, OCF₃, halogen, C₁–C₆ alkyl or C₁–C₆ alkoxy;

n is 0–4;

R₉ is C₁–C₆ alkyl, C₃–C₆ cycloalkyl, OCF₃, OCHF₂, OCH₂F, halogen, CONR₆R₇, CN, CF₃, OH, C₁–C₆ alkoxy, NR₆R₇, SO₃CH₃, SO₃CF₃, SO₂NR₆R₇, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C₁–C₆ alkyl, or COR₈; wherein R₆, R₇ and R₈ are as defined above,

wherein the compound is an (R)-enantiomer, an (S)-enantiomer, or a racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof.

2. The compound according to claim 1 wherein Y is NR_2CO or CONR_2 .

3. The compound according to claim 1 wherein X is N.

4. The compound according to claim 1 wherein R_1 is H or $\text{C}_1\text{--C}_6$ alkyl.

5. The compound according to claim 1 wherein R_3 is $(\text{CH}_2)_n$ -aromatic ring.

6. A compound according to claim 5 wherein the aromatic ring of substituent R_3 is substituted with R_4 , and R_4 is an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from the group consisting of N, O and S; or COR_8 .

7. The compound according to claim 5 or 6 wherein n is 0.

8. The compound according to claim 6 wherein R_8 is NR_9R_7 or a heterocyclic ring containing two heteroatoms selected from N and O.

9. The compound according to claim 1 wherein R_9 is $\text{C}_1\text{--C}_6$ alkyl, OCHF_2 , halogen or $\text{C}_1\text{--C}_6$ alkoxy.

10. The compound according to claim 1 wherein X is N, Y is NR_2CO and R_9 is $\text{C}_1\text{--C}_6$ alkoxy.

11. The compound according to claim 6 wherein X is N, Y is NR_2CO , R_4 is morpholino or COR_8 and R_9 is $\text{C}_1\text{--C}_6$ alkoxy.

12. The compound according to claim 1 wherein X is N, Y is NR_2CO and R_9 is $\text{C}_1\text{--C}_6$ alkyl.

13. The compound according to claim 6 wherein X is N, Y is NR_2CO , R_4 is morpholino or COR_8 and R_9 is $\text{C}_1\text{--C}_6$ alkyl.

14. The compound according to claim 1 wherein X is N, Y is CONR_2 and R_9 is $\text{C}_1\text{--C}_6$ alkoxy.

15. The compound according to claim 6 wherein X is N, Y is CONR_2 , R_4 is morpholino or COR_8 and R_9 is $\text{C}_1\text{--C}_6$ alkoxy.

16. The compound according to claim 1 wherein X is N, Y is CONR_2 and R_9 is $\text{C}_1\text{--C}_6$ alkyl.

17. The compound according to claim 6 wherein X is N, Y is CONR_2 , R_4 is morpholino or COR_8 and R_9 is $\text{C}_1\text{--C}_6$ alkyl.

18. A compound according to claim 1, wherein the compound is (S)-N-[8-Methyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-yl]-4-(dimethylaminocarbonyl)benzamide or N-(4-Morpholinophenyl)-8-methoxy-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2H-1-benzopyran-3-carboxamide in the form of a free base or pharmaceutically acceptable salt or solvate thereof.

19. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound according to claim 1, wherein the compound is an enantiomer or racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof optionally in association with diluents, excipients or inert carriers.

20. A method for the treatment of 5-hydroxytryptamine mediated disorders, comprising administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical formulation of claim 19.

21. A method for the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders,

pain, hypertension, urinary incontinence or vasospasm; or for inhibiting tumor growth, comprising administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical formulation of claim 19.

22. A method for the treatment of disorders in the central nervous system, comprising administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical formulation of claim 19.

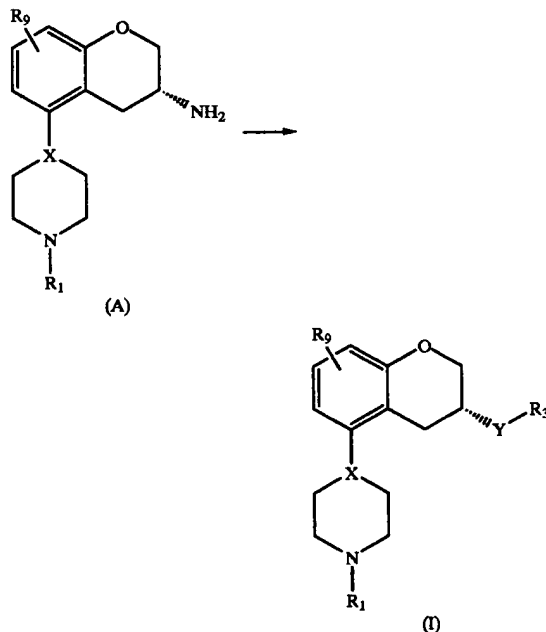
23. A method for the treatment of disorders in the central nervous system and/or urinary incontinence or vasospasm, or for inhibiting tumor growth, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound defined in claim 1.

24. A method according to claim 22 or 23 wherein the disorders of the central nervous system are mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders, pain or hypertension.

25. A method for the treatment of 5-hydroxytryptamine mediated disorders, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound defined in claim 1.

26. A process for the preparation of the compound of formula I according to claim 1, comprising:

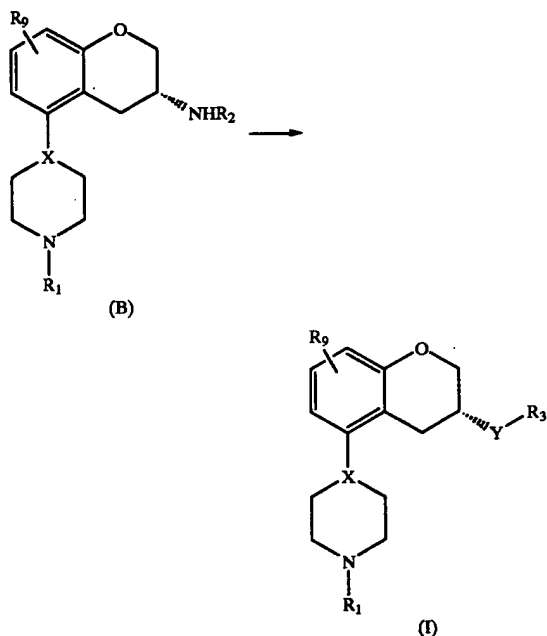
A(i) acylation in the case wherein R_1 is $\text{C}_1\text{--C}_6$ alkyl or $\text{C}_3\text{--C}_6$ cycloalkyl, Y is NR_2CO , R_2 is hydrogen and X, R_3 and R_9 are as defined claim 1, of a compound of formula A



with an activated carboxylic acid $\text{R}_3\text{--COLg}_1$ wherein Lg_1 is a leaving group or with a carboxylic acid $\text{R}_3\text{--COOH}$ and an activating reagent;

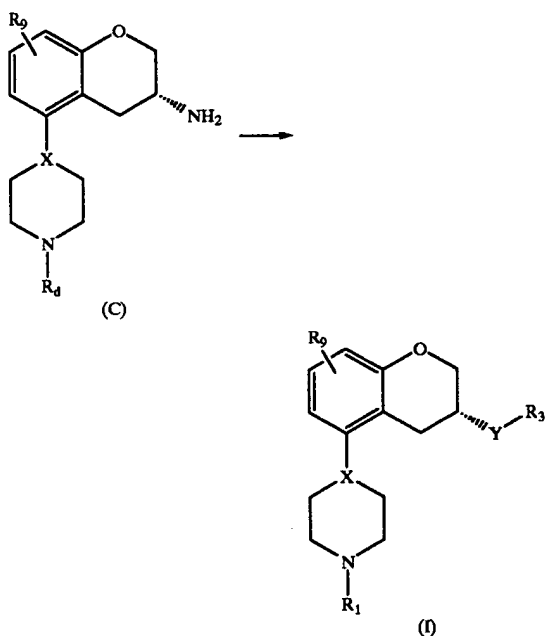
A(ii) acylation, in the case wherein R_1 is $\text{C}_1\text{--C}_6$ alkyl or $\text{C}_3\text{--C}_6$ cycloalkyl, Y is NR_2CO , R_2 is $\text{C}_1\text{--C}_6$ alkyl and X, R_3 and R_9 are as defined in claim 1, of a compound of formula B

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with an activated carboxylic acid $R_3\text{---COLg}_1$ wherein Lg_1 is a leaving group or with a carboxylic acid $R_3\text{---COOH}$ and activating reagent;

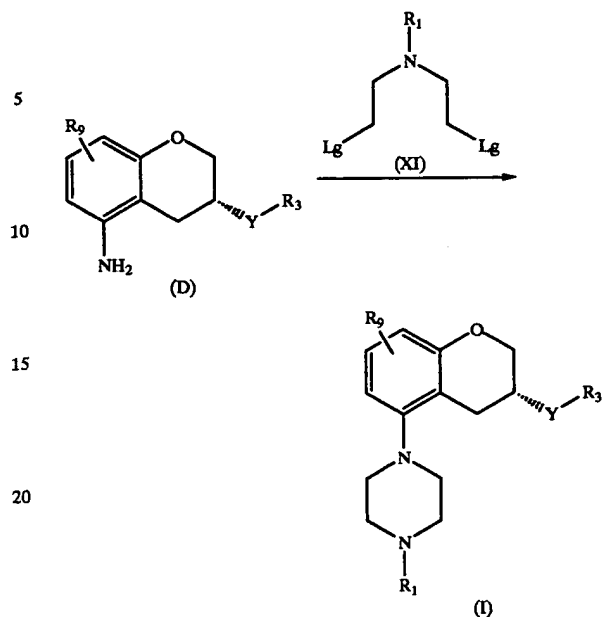
A (iii) acylation, in the case wherein R_1 and R_2 are hydrogen, Y is NR_2CO , R_d is a protecting group and X, R_3 and R_9 are as defined in claim 1, of a compound of formula C



with an activated carboxylic acid $R_3\text{---COLg}_1$ wherein Lg_1 is a leaving group or with a carboxylic acid $R_3\text{---COOH}$ and an activating reagent, and removing the protecting group R_d ;

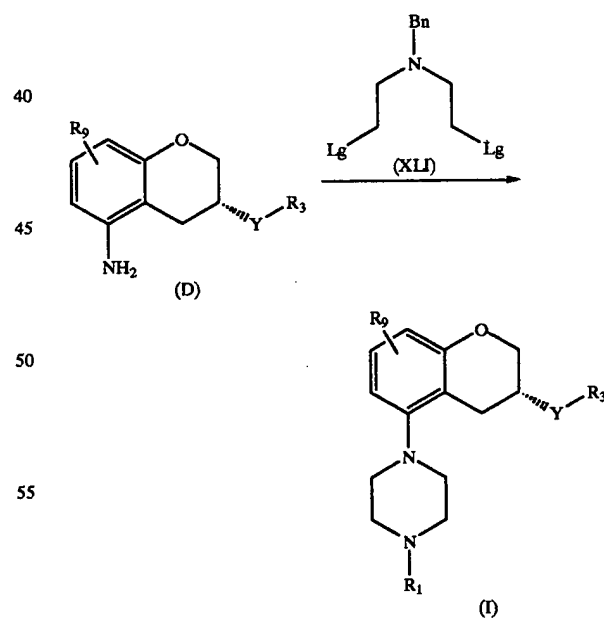
B (i) reacting, in the case wherein Y is CONR_2 and R_2 , R_3 and R_9 are as defined in claim 1, a compound of formula D

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with a compound of formula XI wherein Lg is a leaving group;

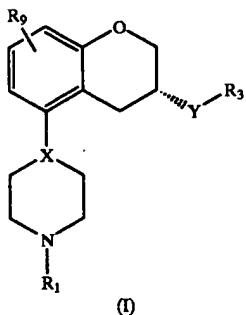
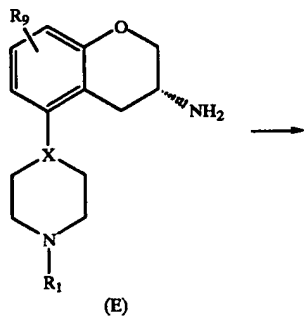
B (ii) reacting, in the case wherein Y is CONR_2 , R_1 is H and R_2 , R_3 and R_9 are as defined in general formula I above with the exception of when R_4 and R_9 are substituents that are susceptible to catalytic hydrogenation known by a person skilled in the art, a compound of formula D



with a compound of formula XLI wherein Lg is a leaving group;

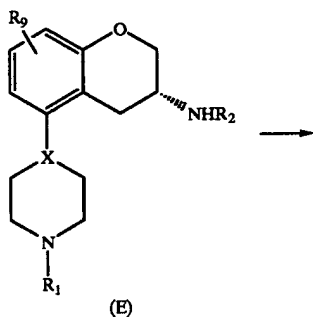
C (i) reacting, in the case wherein Y is NR_2SO_2 , R_2 is hydrogen and R_1 , R_3 and R_9 are as defined in claim 1, a compound of formula E

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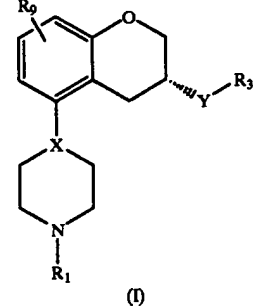
with an appropriate activated sulfonic acid $R_3SO_2Lg_1$, wherein Lg_1 is a leaving group;

C (ii) reacting, in the case wherein Y is NR_2SO_2 , R_2 is C_1-C_6 alkyl and R_1 , R_3 and R_9 are as defined in claim 1, a compound of formula E



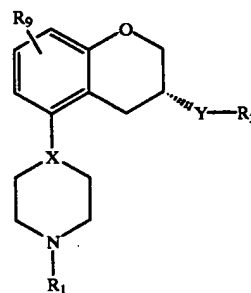
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-continued



with an appropriate activated sulfonic acid $R_3SO_2Lg_1$, wherein Lg_1 is a leaving group;

D reducing a compound of claim 1, wherein Y is $CONR_2$, and X, R_1 , R_2 , R_3 and R_9 are as defined in claim 1 with the exception of when R_4 and R_9 are substituents that are susceptible to certain reducing agents known by a person skilled in the art,



with an appropriate reducing agent to yield a compound of claim 1 wherein Y is CH_2NR_2 , and X, R_1 , R_2 , R_3 , and R_9 are as defined in claim 1.

27. The method according to claim 23 or 25, wherein the mammal is a human.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,387,899 B1
DATED : May 14, 2002
INVENTOR(S) : Berg et al.

Page 1 of 5

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 10,

Lines 50-55, that portion of the formula reading “ NH_2 ” should read NH_2 .

Column 11,

Lines 5-13 and 25-43, (2 instances) that portion of the formula reading “ $\text{N}-(\text{Bn})_2$ ” should read $\text{N}-(\text{Bn})_2$.

Column 12,

Lines 5-25, (2 instances) and 48-65 (2 instances), that portion of the formula reading “ $\text{N}-(\text{Bn})_2$ ” should read $\text{N}-(\text{Bn})_2$.

Column 14,

Lines 1-30 (2 instances), that portion of the formula reading “ $\text{N}-(\text{Bn})_2$ ” should read $\text{N}-(\text{Bn})_2$.

Column 15,

Lines 13-25 and 33-45, that portion of the formula reading “ $\text{N}-(\text{Bn})_2$ ” should read $\text{N}-(\text{Bn})_2$.

Lines 45-60, that portion of the formula reading “ NH_2 ” should read NH_2 .

Column 16,

Lines 23-35, that portion of the formula reading “ $\text{N}-(\text{Bn})_2$ ” should read $\text{N}-(\text{Bn})_2$.

Column 17,

Lines 15-30, that portion of the formula reading “ NH_2 ” should read NH_2 .
Lines 30-43, that portion of the formula reading “ NHCOR_2 ” should read NHCOR_2 .

Column 18,

Lines 3-15, that portion of the formula reading “ NHR_2 ” should read NHR_2 .

Lines 25-50 (2 instances), that portion of the formula reading “ $\text{N}-(\text{Bn})_2$ ” should read $\text{N}-(\text{Bn})_2$.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,387,899 B1
DATED : May 14, 2002
INVENTOR(S) : Berg et al.

Page 2 of 5

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 19,

Lines 5-20, that portion of the formula reading " $\text{N}-(\text{Bn})_2$ " should read $\text{N}-(\text{Bn})_2$:

Lines 20-33, (2 instances) and 40-60 (2 instances), that portion of the formula reading

should read NH_2 :

Lines 58-65, that portion of the formula reading " $\text{CO}_2\text{C}_2\text{H}_5$ " should read $\text{CO}_2\text{C}_2\text{H}_5$:

Column 20,

Lines 1-10, that portion of the formula reading " $\text{CO}_2\text{C}_2\text{H}_5$ " should read $\text{CO}_2\text{C}_2\text{H}_5$:

Lines 35-43, that portion of the formula reading " COOH " should read COOH :

Lines 43-50, that portion of the formula reading " $\text{Y}-\text{R}_3$ " should read $\text{Y}-\text{R}_3$:

Column 21,

Lines 1-10, that portion of the formula reading " $\text{Y}-\text{R}_3$ " should read $\text{Y}-\text{R}_3$:

Lines 33-40, that portion of the formula reading " CO_2R_6 " should read CO_2R_6 :

Column 22,

Lines 10-15, that portion of the formula reading " CO_2H " should read CO_2H :

Column 23,

Lines 3-10, that portion of the formula reading " $\text{CO}_2\text{C}_2\text{H}_5$ " should read $\text{CO}_2\text{C}_2\text{H}_5$:

Lines 13-20, that portion of the formula reading " NH_2 " should read NH_2 :

Lines 40-65 (2 instances), that portion of the formula reading " $\text{N}-(\text{Bn})_2$ " should read $\text{N}-(\text{Bn})_2$:

Column 24,

Lines 23-35, that portion of the formula reading " $\text{N}-(\text{Bn})_2$ " should read $\text{N}-(\text{Bn})_2$:

Lines 38-50, that portion of the formula reading " NH_2 " should read NH_2 :

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 25,

Lines 5-18, that portion of the formula reading “ NH_2 ” should read NHR_2 ;

Lines 30-43, that portion of the formula reading “ $\text{N}-(\text{Bn})_2$ ” should read $\text{N}-(\text{Bn})_2$;

Column 26,

Lines 1-13, that portion of the formula reading “ NH_2 ” should read NH_2 ;

Lines 15-26, that portion of the formula reading “ $\text{Y}-\text{R}_3$ ” should read $\text{Y}-\text{R}_3$;

Lines 55-65, that portion of the formula reading “ NH_2 ” should read NH_2 ;

Column 27,

Lines 1-13 and 50-60, that portion of the formula reading “ $\text{Y}-\text{R}_3$ ” should read



Lines 38-50, that portion of the formula reading “ NH_2 ” should read NH_2 ;

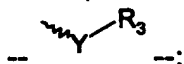
Column 28,

Lines 25-40 (2 instances), that portion of the formula reading “ $\text{Y}-\text{R}_3$ ” should read



Column 29,

Lines 1-25, (2 instances), that portion of the formula reading “ $\text{Y}-\text{R}_3$ ” should read



Lines 55-65, that portion of the formula reading “ NH_2 ” should read NH_2 ;

Column 30,

Lines 1-13 and 40-50, that portion of the formula reading “ $\text{Y}-\text{R}_3$ ” should read



Lines 27-38, that portion of the formula reading “ NHR_2 ” should read NHR_2 ;


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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:



Column 31,

Lines 1-13 and 40-53, that portion of the formula reading “” should read

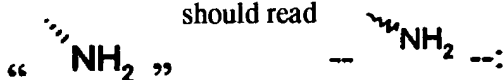


Lines 30-40, that portion of the formula reading “” should read --  --;


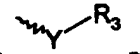
Column 32,

Lines 13-25, that portion of the formula reading “” should read --  --;

Lines 48-60, (2 instances) and 40-60 (2 instances), that portion of the formula reading





Column 33,


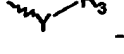
Lines 1-10, that portion of the formula reading “” should read --  --;

Column 40,


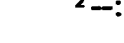
Line 40, delete “soup” and substitute therefor -- group --.


Column 42,

Lines 35-45, that portion of the formula reading “” should read --  --;


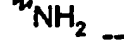
Lines 45-58, that portion of the formula reading “” should read --  --;

Column 43,

Lines 1-13, that portion of the formula reading “” should read --  --;

Lines 15-25 and 48-60, that portion of the formula reading “” should read



Lines 35-45, that portion of the formula reading “” should read --  --;

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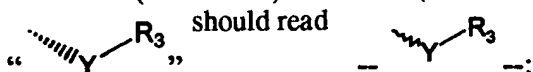
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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 44.

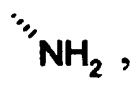
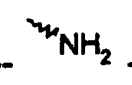
Lines 1-25 (2 instances) and 40-60 (2 instances), that portion of the formula reading







Line 28, insert -- R₁ is as defined in claim 1 -- before the semicolon.

Lines 31-32, delete “general formula I above” and substitute therefor -- claim 1 --.


Column 45.

Lines 1-13, that portion of the formula reading “  ” should read --  --;

Lines 15-25, that portion of the formula reading “  ”, should read --  --;

Lines 35-45, that portion of the formula reading “  ”, should read --  --;

Column 46.

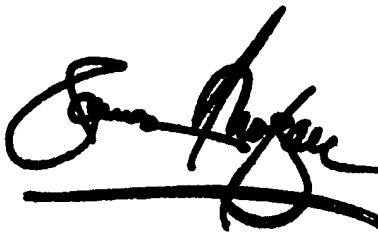
Lines 1-13 and 25-38, that portion of the formula reading “  ”, should read



Signed and Sealed this

Eighth Day of October, 2002

Attest:



Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office